cis-Dihydroxylation and Epoxidation of Alkenes by Manganese Catalysts - Selectivity, Reactivity and Mechanism

Boer, Johannes Wietse de

Chapter 8
General discussion and future prospects

The results of the research described in this thesis are discussed in relation to the requirements for new oxidation catalysts as stated in the preface. Focus is on the major issues encountered, solutions and possibilities for future developments.

As stated in the preface, the goal of the research described in this thesis was to develop new catalysts for the selective oxidation of alkenes. The requirements were not only to develop catalysts capable of activating environmentally benign terminal oxidants such as H_2O_2 or O_2 but that the catalysts themselves should be based on relatively non-toxic and cost-effective metals also; preferably first-row transition metals. In order to be synthetically useful, the catalysts should exhibit high activity, selectivity and robustness.

A problem with the combination of H_2O_2 and first-row transition metal (complexes) is often that catalase type activity occurs. That is, the metal salt or metal complex catalyses the disproportionation of the oxidant H_2O_2 into O_2 and H_2O. Depending upon the degree of the competing catalase-type activity with respect to oxidation catalysis a (large) excess of H_2O_2 is needed to attain full conversion of the substrate. Also with the complex $[Mn^{IV}_2(\mu\text{-}O)_3(tmtacn)_2]^{2+}$ **1** catalase-type activity occurs in addition to oxidation of (alkene) substrates.[1]

The complex $[Mn^{IV}_2(\mu\text{-}O)_3(tmtacn)_2]^{2+}$ is a versatile catalyst for oxidative transformations. It satisfies with the requirements mentioned above: manganese is a first-row transition metal and both the tmtacn ligand and the complex can be (and actually are) produced on large scale and are sufficiently cost-effective to see application in consumer products.[2] However, despite the activity of many groups using Mn-tmtacn based catalysts, mainly for the epoxidation of alkenes (and in many of those cases additives are used to suppress the catalase-type activity), a solid mechanistic insight into the mode of action of the Mn-tmtacn catalysts and into the mode of action of the additives used was much lacking at the outset of the research described in this thesis.

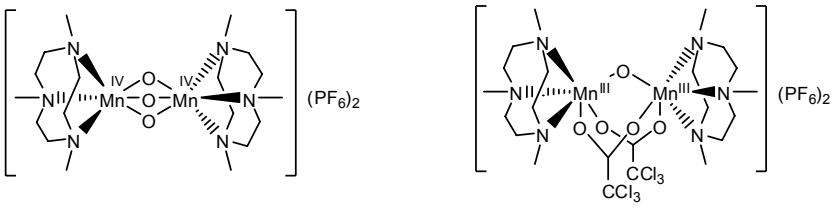
In our group electron-deficient aldehydes had been identified as useful additives for Mn-tmtacn catalysed oxidation of alkenes.[3] Not only did the presence of 25 mol% of aldehyde suppress the catalase type activity, it also induced *cis*-dihydroxylation in addition to epoxidation. However, the role of this additive was not understood.

At the start of the studies described in this thesis it became apparent that it is not the aldehyde which is the active additive. As discussed in Chapter 3, carboxylic acids are the actual additives responsible for the suppression of catalase-type activity and for the activity of the catalysts involved in the Mn-tmtacn catalysed *cis*-dihydroxylation and epoxidation of alkenes. By changing the carboxylic acid, both the activity and selectivity of the Mn-tmtacn catalysed oxidation of alkenes can be tuned. The activity of the catalytic system could be improved by employing electron-withdrawing substituents in the carboxylic acid. Furthermore, the use of salicylic acid as an additive results in preferential epoxide formation, while the use of 2,6-dichlorobenzoic acid results in preferential *cis*-dihydroxylation under otherwise similar reaction conditions.

Although these results were promising, two phenomena showed that the catalytic performance was not yet optimal. First of all, towards the end of the reaction the *cis*-diol product formed initially was (partly) converted to another compound (*i.e.* the corresponding α-hydroxyketone). This overoxidation decreased the yield of the desired *cis*-diol product, but this overoxidation could be suppressed almost completely by maintaining a pseudo

steady-state concentration of the alkene substrate.[i] Secondly, a lag period was encountered where conversion of the substrate did not occur. In order to solve the latter problem, the solution chemistry of the Mn-tmtacn complexes had to be understood.

Thus, despite the identification of carboxylic acids as the active addititive and the ability to tune the selectivity of the catalyst by changing the carboxylic acid, the mode of action of these carboxylic acid additives was not understood. On first sight this might appear of purily intellectual interest. However, the understanding of the mode of action of the carboxylic acid additives and of the solution chemistry of the Mn-tmtacn complexes proved to be key to tackling important issues regarding catalytic performance.



1 **2a**

Figure 8.1 $[Mn^{IV}_2(\mu\text{-}O)_3(tmtacn)_2]^{2+}$ **1** and $[Mn^{III}_2(\mu\text{-}O)(\mu\text{-}CCl_3CO_2)_2(tmtacn)_2]^{2+}$ **2a**.

Speciation analysis of the reaction mixture during the catalytic oxidation reaction showed that at the end of the lag period the complex $[Mn^{IV}_2(\mu\text{-}O)_3(tmtacn)_2]^{2+}$ **1** is no longer present and is converted mainly to the complex $[Mn^{III}_2(\mu\text{-}O)(\mu\text{-}RCO_2)_2(tmtacn)_2]^{2+}$ **2a** (Figure 8.1). The latter complex, containing two bridging carboxylato ligands, remains the major species in solution during the period over which catalytic activity is observed. The identification of these Mn^{III}_2-bis(carboxylato) complexes allowed for the rationalisation of the change in activity and selectivity observed when different carboxylic acid additives are used in combination with **1**. Actually the (bridging) ligands of the manganese dimers are being varied when using different carboxylic acid additives, thus tuning the activity and selectivity of the catalyst.

However, when this newly identified complex $[Mn^{III}_2(\mu\text{-}O)(\mu\text{-}RCO_2)_2(tmtacn)_2]^{2+}$ **2a** was used as catalyst, the lag period decreased only partially, and although the catalytic activity was initially similar to the system **1**/carboxylic acid, during the second half of the reaction, catalyst **2a** lost its activity gradually and eventually all catalytic activity ceased. Full stability of the catalyst throughout the full time course of the reaction could be attained by employing a slight excess of carboxylic acid in solution (Figure 8.2). In this way the equilibrium between the bound, bridging carboxylato ligand and free carboxylic acid is shifted towards the former, ensuring catalyst integrity and thus catalytic activity.

[i] This implies that the overoxidation is not an inherent problem of the catalyst selectivity and, moreover, that by immobilisation of the Mn-tmtacn catalyst on a solid support in a continuous flow reactor good selectivities would in principle be obtained.

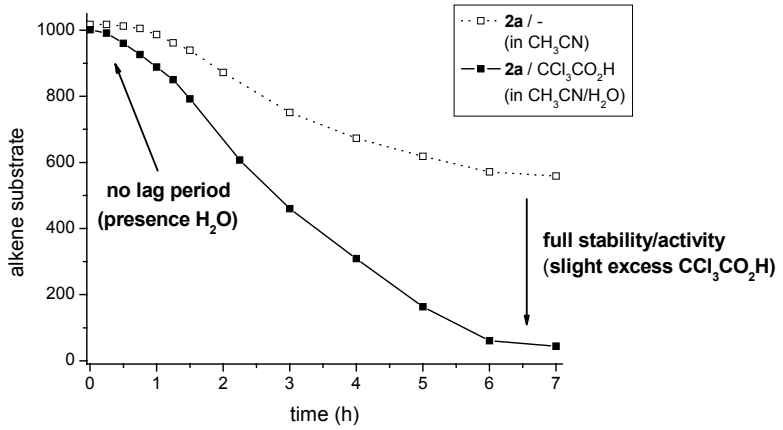


Figure 8.2 Catalytic oxidation of cyclooctene by **2a** (0.1 mol%) without H_2O pretreatment and in the absence of CCl_3CO_2H (dotted line) and with H_2O pretreatment and with CCl_3CO_2H (1 mol%) present (solid line).

The reason for the incomplete reduction of the lag period is more subtle. When the corresponding Mn^{II}_2-bis(carboxylato) complexes were used as the catalyst source, the lag period was suppressed completely and high activity was obtained during the full time course of the reaction. The selectivity during the initial period of the reaction on the other hand (*i.e.* the *cis*-diol/epoxide ratio) was different then during the remainder of the reaction. The differences in both activity and selectivity during the initial period of the reaction (*i.e.* during the 'lag period') are, however, not due to the differences in oxidation state of the manganese dimers (whenever catalytic activity is observed, Mn^{III}_2-bis(carboxylato) complexes are the major species in solution). The crucial factor for the differences in selectivity is the presence of water in the reaction mixture. Together with the oxidant H_2O_2, which is added slowly, water is added and its concentration thus increases over the time course of the reaction. When some water is added prior to starting the reaction, the selectivity observed is normal, together with full activity of the catalyst throughout the reaction, thus making use of the full potential of the catalytic system (Figure 8.2).

This effect of water can be understood in terms of the equilibrium between two Mn^{III}_2-bis(carboxylato) complexes with different non-carboxylato ligands: the 'closed' species **2a** contains a μ-oxo bridge, while the 'open' species **2d** contains two terminally bound hydroxo ligands (Figure 8.3). Since these are more labile then a μ-oxo bridge, ligand exchange with the oxidant H_2O_2 occurs more readily. The presence of water thus improves the activity of the catalyst.

The two important aspects about the proposed catalytic cycle are i) that dinuclear species are involved and ii) that a peroxo species, Mn^{III}_2-η^1-OOH, is proposed to be the catalytically active species that interacts with the alkene substrate to yield the *cis*-diol and

epoxide products.[ii] Coordination of H_2O_2 to the Mn^{III} center polarizes the O-O bond of the peroxide and this polarisation is further enhanced by intramolecular hydrogen bond formation with the hydroxo ligand on the adjacent Mn^{III} center. The present model would be a good starting point for DFT calculations to further explore its validity to the Mn-tmtacn catalysed oxidations and deepen the understanding of the factors governing the activity and the selectivity of the current catalytic system.

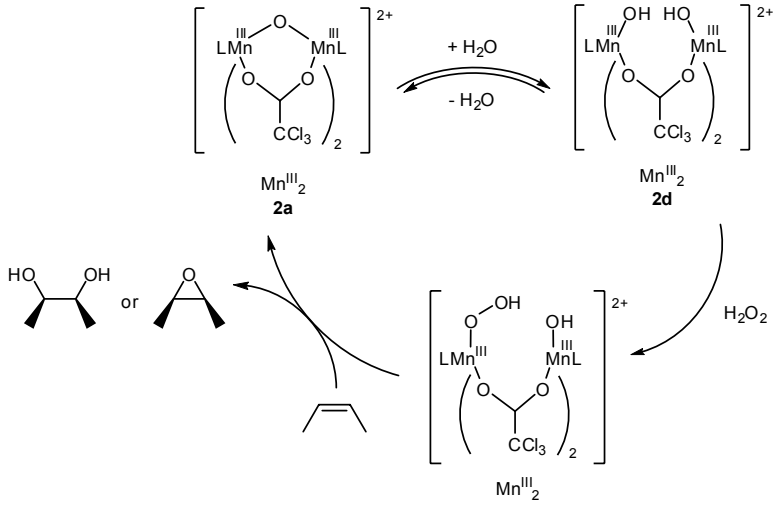


Figure 8.3 Catalytic cycle.

The role of the carboxylic acid additive is threefold: i) it acts as a proton source to protonate one of the μ-oxo bridges of **1**, thus enabling reduction and subsequent ligand exchange, ii) it acts as ligand in the dinuclear Mn^{III}_2 bis(carboxylato) species, thus tuning the activity and selectivity of the catalyst, and iii) slight excess of carboxylic acid in solution improves catalyst stability by suppressing the dissociation of the carboxylato ligands from the Mn^{III}_2 complexes. This, together with the observation that water is needed in the reaction mixture to improve the activity of the system, highlights the need to consider the whole system, instead of just the starting complexes, to improve catalytic performance. Moreover, it is important to consider that one component or parameter can have more than a single role to play. By taking an integrated approach between ('macroscopic') catalytic studies (systematically varying reaction conditions and monitoring changes in reactivity and product distribution in time) and by investigation of the solution chemistry of the manganese complexes involved, the activity and selectivity of the catalytic system could be enhanced and the mechanistic framework for the mode of action of the Mn-tmtacn catalysed oxidation of alkenes could be improved substantially.

[ii] Prior to the start of the studies reported in this thesis, mononuclear, high-valent Mn-oxo species were proposed to be responsible for the catalytic activity observed, despite the, at best, very limited experimental data to support these proposals (for a more detailed discussion of the previously proposed catalytically active species see section 5.4.2.1, Chapter 5 and references cited herein). However, the occurrence of high-valent Mn-oxo intermediates does not fit with the observed ^{18}O-labelling studies and mononuclear complexes have not been observed.

The research described in this thesis provides for the first time detailed experimental evidence for the role of (carboxylic acid) additives in Mn-tmtacn catalysed oxidation reactions. However, analysis of the literature clearly shows that carboxylato/carboxylic acid is present in most experimental procedures described for Mn-tmtacn catalysed oxidation reactions, strongly suggesting that the investigations and phenoma described and the mechanism proposed in this thesis hold direct relevance for Mn-tmtacn catalysed oxidations in general. In particular the importance of (two) bridging carboxylato ligands between two manganese centers as a structural motif and design requirement for manganese based oxidation catalysts is warranted.[4]

The importance of carboxylato ligands/carboxylic acids in Mn-tmtacn catalysed oxidative transformations is illustrated in the experimental procedures described in the referenced articles in a recent review.[iii] Of the 32 references cited concerning Mn-tmtacn catalysed oxidation employing H_2O_2, in 17 papers (53 %) carboxylic acids or carboxylato buffers are used as additive, 4 papers (13 %) report the use of either Mn^{II} or Mn^{III} acetato salts as manganese precursor, 7 papers (22 %) report acetone as solvent, 2 papers (6 %) report the use of a substrate which contains a carboxylic acid group itself and 1 paper (3 %) reports the use of a Mn^{III}_2 bis(carboxylato) complex. It is likely that the combination of H_2O_2 and acetone can result in the formation of acetic acid via Baeyer-Villiger[5] type reaction and thus, effectively, a carboxylic acid is also present when acetone is used as solvent and no carboxylic acid is added deliberately. Indeed, the formation of acetic acid was noted by De Vos and coworkers in a footnote in their report[6] on the Mn-tmtacn catalysed epoxidation of alkenes employing H_2O_2 in acetone.[iv]

Both the identification and the understanding of the role of carboxylic acid additives in Mn-tmtacn catalysed oxidation of alkenes paved the way for the development of the first Mn-based enantioselective *cis*-dihydroxylation catalyst.[v] Again, the understanding of the processes occurring in solution proved to be key to solving the initially low catalyst activity. The recognition that the presence of water liberates the carboxylic acid additive from the esters formed *in situ* was important to maintain the presence of a slight excess of carboxylic acid in solution with respect to Mn^{III}_2-dimer and thus ensures stability and activity of the catalyst.

The combination of **1** and achiral or chiral carboxylic acids, discovery and development of which are described in this thesis, hold considerable potential. Regarding epoxidation, the system **1**/salicylic acid is an attractive system compared with current systems because of its robustness and its ability to employ H_2O_2 as oxidant effectively, thus constituting a clean and environmentally benign method to synthesise epoxides. However, to find broad

---

[iii] Sibbons, K. F.; Shastri, K.; Watkinson, M. *Dalton Trans.* **2006**, 645-661. This review was chosen to provide an unbiased data set of the most relevant Mn-tmtacn literature.

[iv] Similarly, the formation of acetic acid from acetone and H_2O_2 in the presence of $[Fe^{II}(tpa)](OTf)_2$ was observed also: Mairata i Payeras, M.; Ho, R. Y. N.; Fujita, M.; Que, Jr., L *Chem. Eur. J.* **2004**, *10*, 4944-4953.

[v] Although one other Os-free system for the catalytic enantioselective *cis*-dihydroxylation of alkenes, based on Fe, is known [Costas, M.; Tipton, A. K.; Chen, K.; Jo, D.-H.; Que, Jr., L. *J. Am. Chem. Soc.* **2001**, *123*, 6722-6723], the current Mn-system exhibits much higher turnover numbers and catalyst stability.

applicability this system needs to be developed into a catalytic system which exhibits high enantioselectivity.

Of particular significance are the newly developed systems **1**/2,6-dichlorobenzoic acid and **1**/Ac-D-Phg-OH. The former is the most active Os-free *cis*-dihydroxylation catalyst know to date and, moreover, employs H_2O_2 as oxidant. With the latter catalytic system modest enantioselectivity has been obtained (up to 47% *ee*). Although this is far less then the *ee*'s typically obtained with Os-based catalysts and the enantioselectivity of this new system should be improved substantially, these results constitute a major breakthrough since this catalyst is based on a relatively non-toxic and cheap metal, employs H_2O_2 as oxidant and is more robust than the Fe-based systems availlable currently (see section 1.2.2, Chapter 1).

The studies presented in this work indicate that further work should focus on the development of several complementary catalytic systems to cover all substrate classes and the several types of oxidative transformation (*e.g. cis*-dihydroxylation, epoxidation, alcohol oxidation or C-H bond activation). Especially in light of the need to develop *selective* catalysts, it is perhaps naive to imagine that a single catalytic system 'can do it all', *i.e.* be capable of multiple oxidation reactions and be selective simultaneously.

The carboxylato-bridged dinuclear manganese structure should be considered as a potentially key structural motif for the design of new catalytic systems. In addition to the Mn-tmtacn family of catalysts, carboxylate salts or carboxylic acids are often present and their role has received little attention. Examples include compounds such as $[Mn^{III}_2(\mu\text{-}O)(\mu\text{-}CH_3CO_2)_2(tptn)]^{2+}$ [4a,b] and the dinuclear manganese complexes based on the ligand N2PyMePhOH[4c], where a remarkable shift between catalase activity and catalytic oxidation has been observed upon change of the bridging ligands. While the exact mechanism by which these catalysts operate is poorly understood, the similarities of these complexes with Mn-tmtacn in terms of core structure are obvious and the role of both the bridging carboxylato ligands and the other bridging units in these complexes deserves further exploration.

References

[1] Hage, R.; Iburg, J. E.; Kerschner, J.; Koek, J. H.; Lempers E. L. M.; Martens R. J.; Racherla, U. S.; Russell S. W.; Swarthoff, T.; van Vliet M. R. P.; Warnaar, J. B.; van der Wolf, L.; Krijnen, B. *Nature* **1994**, *369*, 637-639.

[2] Hage, R.; Lienke, A. *J. Mol. Catal. A.: Chem.* **2006**, *251*, 150-158.

[3] Brinksma, J.; Schmieder, L.; Van Vliet, G.; Boaron, R.; Hage, R.; De Vos, D. E.; Alsters, P. L.; Feringa, B. L. *Tetrahedron Lett.* **2002**, *43*, 2619-2622.

[4] a) Brinksma, J.; Hage, R.; Kerschner, J.; Feringa, B. L. *Chem. Commun.* **2000**, 537-538. b) Brinksma, J.; La Crois, R.; Feringa, B. L.; Donnoli, M. I.; Rosini, C. *Tetrahedron Lett.* **2001**, *42*, 4049-4052. c) La Crois, *R. M. Manganese Complexes as Catalysts in Epoxidation Reactions: a Ligand Approach*, Ph.D. thesis, University of Groningen, The Netherlands, **2000**. d) de Boer, J. W.; Browne, W. R.; Feringa, B. L.; Hage, R. *C. R. Chimie* **2007**, *10*, 341-354.

[5] March, J. *Advanced Organic Chemistry: Reactions, Mechanisms and Structure* (fourth edition), **1992**, Wiley, New York, pp. 1098-1099.

[6] De Vos, D. E.; Sels, B. F.; Reynaers, M.; Rao, Y. V. S.; Jacobs, P. A. *Tetrahedron Lett.* **1998**, *39*, 3221-3224.